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## Functional Dyspepsia: Recent Advances In Pathophysiology

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### Summary

*Functional (non-ulcer) dyspepsia is a common disease. With effective treatment now available for peptic ulcer; functional dyspepsia remains a major therapeutic challenge in gastrointestinal medicine. Despite advances in technology and diagnostic methods, the "true" underlying pathogenic abnormality in this disease remains elusive. It is likely that functional dyspepsia is a heterogeneous disorder with multiple aetiological factors. In this article various pathophysiological abnormalities in functional dyspepsia are discussed, and possible aetiological mechanisms proposed. (HK Pract 1998;20:327-334)*

### 摘要

功能性消化不良症狀是一種常見疾患，隨著消化性潰瘍治療的進展，功能性消化不良症已成為胃腸科疾患的主要難題。雖然現代技術與診斷方法大為改進，功能性消化不良症的實際病因仍未明瞭。根據現時資料，功能性消化不良症屬多源性的疾患。本文對功能性消化不良症的病理生理性異常及可能病因作詳細討論。

### Introduction

The discovery of *Helicobacter pylori* and effective treatments for peptic ulcer disease has resulted in a focusing of research activity into functional dyspepsia, a common condition with limited therapeutic options. Functional (non-ulcer) dyspepsia is a term generally applied to patients who have chronic

dyspepsia where oesophagogastroduodenoscopy, considered the gold standard test, has excluded peptic ulceration, reflux oesophagitis and malignancy.<sup>1,2</sup> Patients with non-erosive gastritis and duodenitis, by convention, are not excluded. The currently accepted "Rome definition of dyspepsia", based on the consensus opinion of an international panel of clinical investigators, is persistent or recurrent pain or discomfort centered

in the upper abdomen<sup>1</sup> (Table 1). Discomfort, in this context, may be characterised by symptoms such as early satiety, postprandial discomfort or fullness, bloating or nausea. On the other hand, symptoms referable to the oesophagus alone, such as heartburn or acid regurgitation, are no longer considered to constitute part of the definition; although patients with dyspepsia may concurrently have typical reflux-like symptoms.<sup>1,2</sup>

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Table 1: Definitions in dyspepsia

Functional dyspepsia	Pain or discomfort centered in the upper abdomen; and no clinical, biochemical or ultrasonographic evidence of known organic disease that is likely to explain the symptoms.
Ulcer-like dyspepsia	Three or more of the following are necessary, but upper abdominal pain must be a predominant complaint: <ol style="list-style-type: none"> <li>1. Pain that is well localized in the epigastrium (i.e. can be localized to a single small area by pointing with one or two fingers);</li> <li>2. Pain relieved by food, often (more than 25% of the time);</li> <li>3. Pain relieved by antacids and/ or H<sub>2</sub> blockers, often;</li> <li>4. Pain occurring before meals or when hungry, often;</li> <li>5. Pain that at times wakes the patient from sleep;</li> <li>6. Periodic pain with remissions and relapses (periods of at least 2 weeks with no pain interspersed with periods of weeks to months when there is pain).</li> </ol>
Dysmotility-like dyspepsia	Pain is not a dominant symptom. Upper abdominal discomfort should be present in all cases. This discomfort should be chronic and characterized by three or more of the following: <ol style="list-style-type: none"> <li>1. Early satiety;</li> <li>2. Postprandial fullness;</li> <li>3. Nausea;</li> <li>4. Retching and/ or vomiting that is recurrent;</li> <li>5. Bloating in the upper abdomen not accompanied by visible distension;</li> <li>6. Upper abdominal discomfort often aggravated by food.</li> </ol>
Reflux-like dyspepsia	Predominant dyspepsia with heartburn or acid regurgitation. Many of these patients may actually have gastroesophageal reflux disease. (See text)
Unspecified dyspepsia (non-specific)	Dyspeptic patients whose symptoms do not fulfil the criteria for ulcer-like, dysmotility-like or reflux-like dyspepsia.

Adapted from Drossman DA, Richter JE, Talley NJ, et al. Diagnostic criteria for functional gastrointestinal disorders (Ref. 40).

The classification of dyspepsia into various subgroups (e.g., dysmotility-like, ulcer-like, or reflux-like)<sup>1,3</sup> has been problematic. There is a considerable overlap in symptoms and patients may simultaneously fall into different

subgroups. Also, symptoms appear to be poor discriminators of organic versus functional disease,<sup>4</sup> and similar responses to treatment with cisapride has been reported in different symptom groups.<sup>5</sup> However, more recent studies indicated that severe and relevant

postprandial fullness, severe vomiting and female sex are predictors of delayed gastric emptying,<sup>6</sup> and reflux-like symptoms may be indicative of increased gastro-oesophageal reflux.<sup>7</sup>

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**Pathophysiology of functional dyspepsia*****Helicobacter pylori*, gastritis and duodenitis**

A population based study examined *H. pylori* positivity in dyspeptics with normal endoscopic findings and normal controls. Although there was a trend for dyspeptics to have a higher infection rate, the differences were not statistically significant.<sup>8</sup> In a Dutch study, the apparent association between *H. pylori* and dyspepsia was due to subjects with a past ulcer history.<sup>9</sup> From another perspective, most studies have failed to demonstrate any significant difference in the symptom pattern in patients with and without the infection.<sup>10,11</sup> Also, *H. pylori* infection does not affect gastric sensitivity,<sup>12</sup> antro-duodenal motility<sup>13</sup> or gastric emptying<sup>14</sup> in dyspeptic patients. Thus, although histological gastritis (usually caused by *H. pylori*) is found in between 30% to 70% of patients with functional dyspepsia,<sup>15,16</sup> it is unlikely to be a significant cause for dyspeptic symptoms.

Several studies have attempted to study the effects of *Helicobacter* eradication, but in many the designs are flawed.<sup>17</sup> There are several reports that *H. pylori* positive dyspeptics receiving successful eradication therapy had less symptoms than non-eradicated controls after 6 to 12 months, although short term response rates were similar in both groups.<sup>18-20</sup> On the other hand, another double-blind 6-month study using a validated

symptom questionnaire showed no difference in dyspeptic symptoms after *Helicobacter* eradication.<sup>21</sup> At the present state of knowledge, no definite link between *H. pylori* gastritis and functional dyspepsia can be established.

**Gastric acid**

A recent study using gastrin releasing peptide as a secretagogue to simulate meal-stimulated acid output suggested that *H. pylori* positive dyspeptics have a higher acid output than asymptomatic infected volunteers.<sup>22</sup> However, most studies have found normal basal and gastrin-stimulated peak acid output in functional dyspeptics, when compared to healthy controls.<sup>23</sup>

Various studies have attempted to reproduce pain with intragastric acid perfusion. Although some patients may experience atypical discomfort, similar symptoms may occur after perfusion of normal saline.<sup>24</sup> Moreover, while patients with functional dyspepsia are more likely to experience pain after pentagastrin injection, blocking of acid secretion did not reduce pain.<sup>25</sup> Acid probably does not play a significant role in the pathogenesis of functional dyspepsia but may be more relevant in the subgroup of dyspeptic patients with reflux-like symptoms.<sup>7</sup>

**Dysmotility**

Delayed gastric emptying<sup>26</sup> and antral hypomotility<sup>27</sup> have been demonstrated in up to 50% of

patients with functional dyspepsia. However, the correlation between dyspeptic symptoms and the gastric emptying rate is poor.<sup>28</sup> More recently, abnormal distribution of solids in the stomach has been demonstrated in patients<sup>29</sup> with increased postprandial accumulation in the distal stomach. Also, a study has reported a lower number of duodenal migrating motor complexes with an increased proportion of time in phase II of the cycle during sleep.<sup>30</sup> However, in most patients studied, there was poor temporal correlation between episodes of pain and abnormal motor activity.

**Altered sensory function**

Recent studies have focused more on abnormal perception in functional gastrointestinal disorders. Decreased perception thresholds to intraluminal distension in the gastric fundus<sup>31-33</sup> and duodenum<sup>34</sup> has been demonstrated in a proportion of patients; and a decreased gastric relaxatory response to duodenal distension has also been observed.<sup>33</sup> It is possible that abnormal fundal tone and gastric relaxation may act synergistically with lowered visceral pain thresholds to produce postprandial pain and bloating in patients.

Increased visceral sensitivity appears to be a generalised phenomenon in the gastrointestinal tract. Dyspeptic patients also have lowered sensory thresholds in the oesophagus and rectum.<sup>35</sup> Interestingly, despite the widespread nature of visceral hypersensitivity, somatic pain thresholds are not affected in

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## Key messages

1. Functional dyspepsia is a common disease with heterogeneous pathophysiology.
2. Although firmly implicated in peptic ulcer disease, the role of *Helicobacter pylori* in functional dyspepsia is less clear. Only some studies have shown a long-term benefit in dyspeptic symptoms after *H. pylori* eradication.
3. Gastric acid is probably not related to dyspeptic symptoms.
4. Dyspeptic patients may have disordered gastrointestinal motility and abnormal fundal tone.
5. Patients may have abnormal visceral hypersensitivity.
6. Increased anxiety and depression are present in dyspeptic patients attending medical clinics.

functional dyspepsia. The pain threshold to transcutaneous nerve stimulation remains normal, despite a lower pain threshold to balloon distension in the stomach.<sup>33</sup>

### Psychosocial factors

Several studies have shown a higher level of anxiety and depression in patients with functional dyspepsia, when compared to healthy controls.<sup>36-38</sup> However, their level of anxiety may not be different from patients with non life-threatening organic bowel diseases.<sup>36,39</sup> Co-existing depression and anxiety may act as a catalyst for a patient to seek medical care, rather than being the cause of symptoms.

### Conclusions

Much advance has been made in the understanding of functional dyspepsia. It is probably hetero-

geneous in nature and the lack of diagnostic markers restrict precise study. It remains to be determined whether the various physiological abnormalities observed are markers of the condition or merely epiphenomena. Truly effective management strategies can only be formulated when the true underlying aetiology has been made clear. ■

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